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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/815,390	03/31/2004	Jayvardhan Pandit	PC25193A	8860

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PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
EASTERN POINT ROAD
GROTON, CT 06340

EXAMINER	
NASHED, NASHAAT T	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 06/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/815,390	PANDIT, JAYVARDHAN	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *12-15 and 17-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/20/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-11 and 16, drawn to a crystal and co-crystal a phosphodesterase 1B (PDE1B), classified in class 435, subclass 196.

II. Claims 12-15, drawn to a computer comprising a data storage system containing the atomic coordinates that defined PDE1B, classified in class D14, subclass 485.

III. Claim 17, drawn to a homology method to construct the three-dimensional structure of a protein homolog of PDE1B using the atomic coordinates disclosed in the application, classified in class 702, subclass 27.

IV. Claims 18 and 19, drawn to a method of identifying a ligand for PDE1B, classified in class 702, subclass 27.

V. Claims 20 and 21, drawn to a method of treating psychological disorder, classification is unknown. Since the classification system is based on chemical structures the specification does not teach or exemplify any ligand of PDE1B, the classification is unknown.

VI. Claim 22, drawn to a vector comprising the catalytic domain of PDE1B, classified in class 435, subclass 320.1.

The inventions are distinct, each from the other because of the following reasons:

Inventions II and I are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are not disclosed as capable of use together. The crystal and the computer can't be used together.

The crystal of inventions I, and the methods of inventions III-V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the methods of inventions III-V do not utilize the crystal of invention I.

Inventions VI and I are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are independent chemical entities and require separate searches in the patent and non-patent literature.

The computer of invention II, and the methods of inventions III and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the computer can be used at least in the two methods of inventions III and IV as well as in a method of identifying mutation sites and word processing.

Inventions II and V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are not disclosed as capable of use together.

Inventions II and VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are not disclosed as capable of use together.

Inventions III-V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are independent methods having different steps and products and effects.

The methods of inventions III-V, and the vector of invention VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the vector of invention VI is not utilized by any of the methods of inventions III-V and it has different uses such as in a recombinant method to make the catalytic domain of PDE1B.

Because these inventions are independent or distinct for the reasons given above and the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

Because these inventions are independent or distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Irene Reininger on May 30, 2006 a provisional election was made with traverse to prosecute the invention of invention I, claims 1-11 and 16. Affirmation of this election must be made by applicant in replying to this Office action. Claim12-15 and 17-22 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The use of the trademarks such as pFastBac-1 and Bac-to-Bac have been noted in this application; see for example page 36, line 21. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see for example at page 39, line 1. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The disclosure is objected to because of the following informalities: (a) "E64" at page 37, lines 1 and 23 is apparently a component of buffer compositions, which is not identified by a proper chemical name and one of ordinary skill in the art would not know what it is; (b) The abbreviation "PDE-1B-13" is not defined in the specification, in particular, the number "13" lack antecedent bases in the specification; and (c) The chemical structure of compound 109 at page 37 line 28; page 7, last paragraph, and Figure 1 is not defined by chemical name.
Appropriate correction is required.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s). In particular, 37 CFR 1.821, which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Thus, each time the references to "human PDE1B" and "PDE1B catalytic doamin" appear in the specification or in the claims, they should be accompanied by SEQ ID NO: 1 and SEQ ID NO: 2, respectively, (see for example see Figures descriptions at pages 30 and 31, and page 36, lines 20-25, and page 37, line 28. Also the headings to Tables 1-3, the Table at page 23. at page 27, lines 1 and 2, there are two amino acid sequences, which are not accompanied by a sequence identification number.

Claim 7 is objected to because of the following informalities: amino acid Thr142 to Gln507 of SEQ ID NO: 1 is defined by SEQ ID NO: 2 in the sequence listing. Applicant must refer the amino acid sequence of residues Thr142 to Gln507 of SEQ ID NO: 1 as SEQ ID NO: 2. Appropriate correction is required.

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 4, 5, and 16 are directed to all possible crystals of any phosphodiesterase 1B (PDE1B) from any biological source or mammal, which include co-crystal with any chemical compound grown under any crystallization conditions. Claims 3, and 6-9 are directed to any crystal or co-crystal of any PDEB1 of SEQ ID NO: 1 or homologue or variants thereof. Claim 10 is directed to any crystalline form for a polypeptide having the amino acid sequence of SEQ ID NO: 1 or homologues or variants thereof. The specification, however, only provides a single representative species of these crystals containing only the amino acid sequence of SEQ ID NO: 2 (the catalytic domain consisting of 142-507, i.e., 366 amino acid residues of of SEQ ID NO: 1) and undefined compound named "compound 109". The crystal is a tetragonal crystal in space group $P4_32_12$, see page 38, lines 23-25. The specification has failed to describe any crystal of any full-length SEQ ID NO: 1 or any other PDE1B from any source.

The court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] name chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." UC California v. Eli Lilly (43 USPQ2d 1398). For claims drawn to genus, MPEP section 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Also, MPEP section 2163 states that a representative number of species mean that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. At the time of invention, the full-length human PDE1B was well known in the art along with variants from other animal. In general, for a species of crystal to be

adequately and structurally described, the following must be adequately described: (i) the exact chemical composition of the crystal, i.e., the structure feature of all molecules in the crystal including the amino acid sequence of any protein or nucleic acid, (ii) the space group of the crystal; and (iii) the unit cell dimension of the crystal. Neither the applicants nor the prior art has described a crystal or the crystallization of the 536 amino acid residues of SEQ ID NO: 1 with or without a ligand. Neither the application or the prior art teach a catalytic domain crystal of PDE1B without a ligand or a ligand other than compound 109. The specification does not identify compound 109 as inhibitor or antagonist and does not teach any other compounds as inhibitors or antagonist. Thus, the specification fails to describe additional representative species of these crystals by any identifying structural characteristics or properties other than the crystal containing the amino acid sequence of SEQ ID NO: 2 having space group and the unit cell dimension cited in at page 38, lines 23-25, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 1-11 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all-possible crystals comprising any full-length or fragments of PDE1B from any biological or man-made source. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any possible crystals comprising any PDE1B or fragments or homologues or variants thereof. The specification provides guidance and examples in the form of an assay to obtain the catalytic domain of human PDE1B of SEQ ID NO: 2 and the crystallization of the polypeptide of SEQ ID NO: 2 with a chemical compound named 109, under specific crystallization conditions (see examples 1-3). While molecular biological techniques and genetic manipulation to make any protein, a general crystallization methods for proteins, and synthetic method to make any compound that binds to PDE1B are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of a particular protein and its complexes is lacking. It is well established

in the art that obtaining a protein and its complexes in a crystal form is highly unpredictable without any clear expectation of success, and any change in a given crystallization condition including any minor alteration could alter the crystal form and its diffraction characteristics or even lack of crystal formation. It is now evident that protein crystallization is the major hurdle in protein structure determination. For this reason, protein crystallization has become a research subject in and of itself, and is not simply an extension of structure biologist or crystallographer's laboratory. There are many references that describe the difficulties associated with protein crystals. See for example, Gilliland *et* al, (*Curr. Open in Struct. Biol.* 1996, 6, 595-603) in particular page 600, left column second paragraph; Ke *et al.* (Methods, 2004, 34, 408-414); and Wiencek, J. M. (Ann. Rev. Biomed. Eng. 1999, 1, 505-534). Thus, the skilled artesian would be expected to screen large number of crystallization conditions, which may include screening variety of conditions in space, a micro gravity environment. A protein which may crystallize under specific crystallization condition, it mutants may or may not crystallize under the same condition. In many cases, a protein that can't be crystallized, one of its specific mutants might be crystallized. Even if a crystal is obtained, it may or may not be suitable for structure determination by X-ray crystallography. Thus, searching for a crystallization conditions for a protein and its complexes that is suitable for X-ray crystallography is well outside the realm of routine experimentation and predictability in the art of success in is extremely low. The amount of experimentation to identify a crystal for a protein having amino acid sequence of SEQ ID NO: 1, or any mutant, fragment, or homologue or variant and obtain a suitable crystal for structure determination X-ray crystallography is enormous. Since routine experimentation in the art does not include screening large number of crystallization conditions or mutants or fragment of SEQ ID NO: 1 which can be crystallized where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the amino acid sequences of the HDM2, the chemical structure of a ligand which is binds to SEQ ID NO: 1 and form the binary complex to be crystallized, and identify a crystallization conditions that produce a crystal suitable for structure determination by X-ray crystallography. Without such guidance, the experimentation left to those skilled in the art is undue.

> The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-6, 8-11 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections of the claims:

(a) The phrase "or a homologue or variant thereof" in claims 3, 6, and 10 renders the claims indefinite because the resulting claims do not set forth

the metes and bound of the desired patent protection. For examination purposes only, the phrase is interpreted to mean any phosphodiesterase from any biological source.

(b) The phrases "phosphodiesterase 1B", "PDE1B" or PDE1b in claims 1-4 and 10 render the claim indefinite because the resulting claims do not set for the metes and bound of the desired patent protection. Although there are many phosphodiesterase are known in the prior art including PDE1B of SEQ ID NO: 1, they are identified by their amino acid sequences. Many of the known cyclic nucleotides phosphodiesterases catalyze cAMP or cGMP or both. Since there is no specific characteristic taught in the specification the differentiate PDE1B from other phosphodiesterse, the phrases "phosphodiesterase 1B", "PDE1B" or PDE1b are assumed to mean any phosphodiesterase.

(c) The phrase "an antagonist or an inhibitor" in claim 5 renders the claim indefinite because the resulting claims do not set forth the metes and bound of the desired patent protection. The examiner does not understand the difference between an antagonist of enzymatic activity and inhibitor of the enzymatic activity. In fact, the word "antagonist" is not used with enzymatic activity. The word "antagonist" is used in the art of receptors where the binding of a small molecule is not accompanied by catalysis of a chemical reaction. Thus, the use of the word "antagonist" in claim 5 is repugnant to one of ordinary skill in the art.

(d) The phrase "compound 109" in claim 8 renders the claim indefinite because the resulting claims do not set forth the metes and bound of the desired patent protection. Compound 109 is not defined by the claim or the specification and one of ordinary skill in the art would not know what is it. For examination purposes only, it assumed to be any chemical compound.

(e) The phrase "or even 0.2" in claim 9 renders the claim indefinite because the resulting claim does not set forth the metes and bound of the desired patent protection. For examination purposes only, the word even is omitted from the claim.

(f) The phrases "consisting essentially of", "catalytic domain", and "PDE1b" in claim 11 render the claim indefinite because the resulting claims do not set forth the metes and bound of the desired patent protection. The "catalytic domain" is indefinite because it is not defined by the specification or the claim, and one of ordinary skill in the art would not know the boundaries of the catalytic domain, which make the phrase "consisting essentially of" indefinite as well. While the specification

identify the abbreviation PDE1B as 3',5'-cyclic nucleotide phosphodiesterase 1B, PDE1b is not defined by the specification or the claims. For examination purposes only, PDEP1b is assumed to be PDE1B.

(g) The phrase "a derivative expressed in any reference frame" in claim 16 renders the claims indefinite because the resulting claims do not set forth the metes and bound of the desired patent protection. The examiner is confused by this phrase, and is almost sure that the phrase does not belong in the claim. Please explain or amend to remove the phrase. For examination purposes only, the phrase is deleted.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-7 and 11 rejected under 35 U.S.C. 102(e) as being anticipated by US2005/0048573 A1 ('573, Artis *et al.*). The '573 document resulted from the publication of U. S. patent application 10/771,833 filed February 3, 2004, which claim priority to provisional application 60/444,734 ('733), filed February 3, 2003. The priority document fully enables a crystalline catalytic phosphodiesterase 5A, which is 99.2% identical to SEQ ID NO: 2 of the instant application.

The '573 patent document teach the amino acid sequence of SEQ ID NO: 17 consisting of 369 amino acid residues, which is 99.2 identical to SEQ ID NO: 2 of the instant application, residues 1-363 of SEQ ID NO: 2 of the instant application are 100% identical to residues 7-369 of SEQ ID NO: 17 of '573 document (claim 11). Also, they teach the catalytic domain of PDE5A, see paragraph 19 at page 4 as well as the expression of said catalytic domain and crystallization with the thiophosphate analougue of cAMP to obtain a crystal suitable for structure determination by the single crystal X-ray diffraction method (claims 1-7), see examples 1-3, pages 33-35.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1656

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